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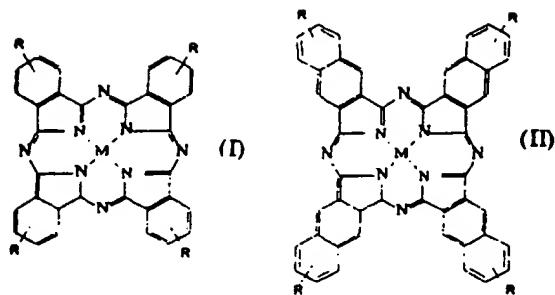
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## (54) AGENT FOR SUPPRESSING TUMOUR GROWTH

(57) The invention pertains to biology and medicine, specifically, to the suppression of malignant tumour growth. The problem addressed by the invention is that of finding more effective and less toxic agents for suppressing tumour growth. The invention in essence proposes the use of a substance consisting of a cobalt or iron complex with substituted phthalocyanines (I) or naphthalocyanines (II) and of a biogenic reducing agent. In the formulae shown, R = COONa, SO<sub>3</sub>Na, CH<sub>2</sub>C<sub>5</sub>H<sub>4</sub>N<sup>+</sup>Cl<sup>-</sup>, CH<sub>2</sub>(NH<sub>2</sub>)<sub>2</sub>S<sup>+</sup>CH<sub>2</sub>Cl<sup>-</sup>. Use of the proposed agent facilitates effective suppression of a wide range of malignant neoplasms, specifically, suppression of malignant cell proliferation (*in vitro*), slowing of tumour growth in mice (*in vivo*), and a significant increase in the life expectancy of the mice by comparison with *inter alia* the use of a prototype.

REF. B1



**Description**

The invention relates to the field of biology and medicine, in particular to suppression of the growth of malignant tumors.

5 The following drugs are known for suppression of tumor growth.

1. Cis-dichlorodiaminoplatinum. Having a wide range of action, it is used for treatment of solid tumors of various localization [1, 2], but exhibits high nephrotoxicity [3].

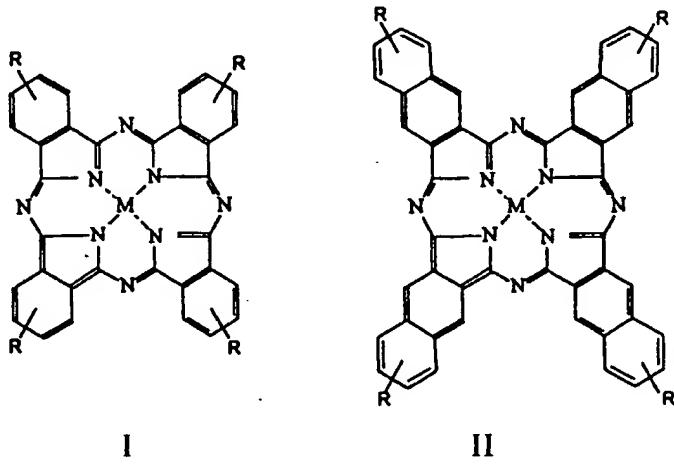
10 2. Photodynamic therapy of tumors, in which photosensitizers — free tetrapyrrolic macrocyclic ligands or their complexes with metals, e.g. aluminum complex of sulfonated phthalocyanine Al[Pc(SO<sub>3</sub>H)<sub>4</sub>] — are used. Their use is only possible in the case of surface located tumors, more exactly - accessible for a laser probe [4].

15 3. A drug consisting of a complex of copper (II) with glycylglycylhistidine tripeptide ([Cu(GGH)]Cl) and sodium salt of ascorbic acid in a ratio of 1:10 is the drug most similar to that proposed; it causes an increase in the life-span (ILS) of mice with Ehrlich ascitic carcinoma [5].

15 Drawbacks of the prototype are low effectiveness related to the low selectivity of that complex in respect of tumors and its instability in physiological conditions, and a high toxicity due to the products of decomposition of the complex.

The object of the present invention is to find more effective and less toxic drugs for suppression of tumor growth.

20 The essence of the proposed invention is that a drug consisting of a biogenic reductant and a complex of cobalt or iron with substituted phthalocyanines (I) or naphthalocyanines (II) is used to suppress tumor growth.



40 where R = COONa, SO<sub>3</sub>Na, CH<sub>2</sub>C<sub>5</sub>H<sub>4</sub>N<sup>⊕</sup>Cl<sup>⊖</sup>, CH<sub>2</sub>(NH<sub>2</sub>)<sub>2</sub>S<sup>⊕</sup> C H<sub>2</sub>Cl<sup>⊖</sup>

The scientific foundation for the invention is literary data on the selective accumulation of tetrapyrrolic macrocyclic compounds and their complexes with metals in tumorous tissues [4, 6] and the facts that we have established which show the high catalytic activity of phthalocyanine complexes of cobalt and iron in model chemical systems, in particular:

45 1) they are homogenic catalysts of the autoxidation row of biogenic reductants and analogues thereof, e.g. ascorbic acid, ubiquinone and cysteine;

2) the (intermediate) formation of active forms of oxygen - the anion-radical of superoxide, hydrogen peroxide and a hydroxyl radical, the cytostatic and other biological activity of which is well known - takes place in this reaction [7];

3) in the conditions of this reaction, the proposed complexes cause an oxidative degradation of nucleic acids.

50 **METHODS AND RESULTS OF TESTS**

Tests of the proposed drug for cytotoxic and antitumor activity were carried out on cultures of tumor cells (in vitro) and on mice with regrafted tumors (in vivo).

Determination of the activity of the drugs on cultures of tumor cells (in vitro)

## Method 1.

5 The method of evaluation of the cytostatic effect of a combination of phthalocyanines with ascorbic acid in a system in vitro was developed on a culture of tumor cells of human testicular carcinoma (Cao V line).

The culture of cells was grown in a monolayer in medium 199 comprising a 10% solution of an embryonic calf serum.

At the beginning of the experiment the cells were inoculated at a density of 100000/ml in a total volume of 2 ml and 10 incubated at 37°C for 24 hours. Then the testing was carried out in the following variants:

## 1. Control.

The growth medium for the samples was replaced with a fresh intact nutrient medium and incubated for 48 hours, then  $^3\text{H}$ -thymidine ( $^3\text{H}$ -T) in a final concentration of 1  $\mu\text{Curie}/\text{ml}$  was introduced into the medium of the samples, it was washed with a Hank's solution, a 2.5% solution of perchloric acid, and the acid-insoluble fraction was hydrolyzed in 5 ml of 5% perchloric acid. The hydrolyzates in a volume of 100  $\mu\text{l}$  were transferred into flasks with a scintillation fluid SF-8 and the level of radioactivity in the samples was registered on a RackBeta (Sweden) fluid scintillation counter. The average values of the level of radioactivity were calculated.

20 2. In order to evaluate the effect of ascorbic acid on the growth of cells of the Cao V line, the growth medium of the samples was replaced with a fresh medium, comprising ascorbic acid in a concentration of  $1 \times 10^{-4}$  M, incubated for 4 hours, and then the sample was processed according to the method described in para 1.

25 3. In order to evaluate the effect of phthalocyanine metal complexes on the growth of cells of the Cao V line, the growth medium of the samples was replaced with a fresh medium, comprising complexes in a predetermined concentration, the method described in para 1 was followed.

4. In order to evaluate the cytostatic effect of the combination of phthalocyanine and ascorbic acid, ascorbic acid was added into the growth medium comprising the complex in a ratio of concentration equal to 1:10, and the method described in para 1 was followed.

The suppression of the  $^3\text{H}$ -T inclusion in the test samples was calculated according to the equation

$$30 \quad (1 - \frac{\text{average value of decomposition/min/test samples}}{\text{average value of decomposition/min/control samples}}) \times 100\%$$

35 Statistic processing of the results was carried out using the method of sample analysis.

## Method 2.

Determination of the cytostatic activity of the drugs being tested was carried out using a biotest based on inhibiting 40 the proliferation of a regrafted culture of cells of human lung adenocarcinoma A-549, due to the action of cytotoxic agents.

In order to cultivate cells of the A-549 line, the Eagle medium was used with the addition of 100  $\mu\text{g}/\text{ml}$  of heptamycin and a 10% solution of embryonic calf serum, preliminarily inactivated by heating. Cultivation of the cells was carried out under standard conditions: at 37°C in a humid atmosphere, comprising 5% carbon dioxide.

45 When a cytostatic biotest was being set up, 100  $\mu\text{l}$  of a suspension of cells of the A-549 line at a concentration of  $7.5 \times 10^4$  cells/ml were placed in each of the craters of a flat 96-crater microboard ("Sarstedt," USA) with addition of the drugs being tested in a volume of 100  $\mu\text{l}/\text{crater}$  at the beginning of the phase of logarithmic growth.

The cytostatic activity of the drugs being tested was evaluated by the colorimetric method, based on the capability of mitochondrial dehydrogenases of live test-cells of restoring exogenetically introduced soluble 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazole bromide (MTT, "Sigma Chemical Co.," USA) into an insoluble crystalline formazan. Wherein, 20  $\mu\text{l}$  of a solution of MTT at a concentration of 5 mg/ml were put into each crater of the 96-crater microboard, after which the cell cultures were centrifuged, the whole volume of the culture medium was removed from the craters. For solubilization of the colored reaction products (crystals of formazan), 150  $\mu\text{l}$  of dimethylsulfoxide ("Sigma") were introduced into each crater of the microboard and the microboard was incubated at room temperature and continuously 55 shaken. The results were registered upon absorption at a wavelength of 550 nm on the minireader "Dynatech" (FRG).

The level of inhibition of proliferation of the cell cultures by the drugs being tested for cytostatic activity was calculated according to the equation:

$$IP(\%) = 100\% - \frac{P_t}{P_c} \times 100\%,$$

5 where:

IP is the level of inhibition of the proliferation;

$P_t$  is the level of proliferation in the test (with the drugs): absorption of the dye in test samples;

$P_c$  is the level of proliferation in the control (without the drugs): absorption of the dye in test samples.

10 Data are presented in Table 1 on the absence of cytotoxic activity of ascorbic acid ( $AH_2$ ) by itself and of phthalocyanine complexes relative to cells of the Cao V and MCF-7 lines at a predetermined criterion of activity  $CE_{50}$  equal to  $10^{-4}$  M for a 48-hour period of incubation.

15 Table 1. Antiproliferation activity of components of the claimed drug  
(phthalocyanine and naphthalocyanine complexes of metals and ascorbic acid)  
relative to tumor cells of a human in vitro

20 Content	CE <sub>50</sub> , M	Human testicular carcinoma	Breast adenocarcinoma
25		CaoV*	MCF-7 line
Co[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]	2.5x10 <sup>-4</sup>		
Fe[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]	2x10 <sup>-4</sup>		
Fe[Pc(COONa) <sub>8</sub> ]	0.5x10 <sup>-4</sup>		
Co[Pc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>6</sub> ]Cl <sup>⊖</sup> <sub>6</sub>	5x10 <sup>-4</sup>		1x10 <sup>-4</sup>
Co[Pc(SO <sub>3</sub> H) <sub>2</sub> ]	5x10 <sup>-4</sup>		1x10 <sup>-4</sup>
Co[Pc(CH <sub>2</sub> (NH <sub>2</sub> ) <sub>2</sub> SCH <sub>2</sub> C <sub>1</sub> ) <sub>8</sub> ]	2.5x10 <sup>-4</sup>		
Co[Nc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>2</sub> ]Cl <sup>⊖</sup> <sub>2</sub>	1x10 <sup>-4</sup>		
Co[Pc(COONa) <sub>8</sub> ]	5x10 <sup>-4</sup>		1x10 <sup>-4</sup>
AH <sub>2</sub>	>1x10 <sup>-3</sup>		>1x10 <sup>-3</sup>

45 \* AH<sub>2</sub> - ascorbic acid

50 The compound was considered to be active if  $CE_{50}$  [the concentration at which a 50% suppression of inclusions <sup>3</sup>H-T in the cells (see method 1)] was  $1x10^{-4}$  M under these conditions of the experiment. As is evident from the presented results, the complex Co[Nc(CH<sub>2</sub>C<sub>5</sub>H<sub>4</sub>N<sup>⊕</sup>)<sub>2</sub>]Cl<sup>⊖</sup><sub>2</sub> and the complex Fe[Pc(COONa)<sub>8</sub>] had limited activity, all the other complexes and AH<sub>2</sub> were inactive.

Data are grouped in Table 2 which were obtained during a study of the inhibition of the proliferation of tumor cells in vitro when phthalocyanines and ascorbic acid were used together in noncytotoxic concentrations.

5 Table 2. Inhibition of the proliferation of tumor cells in the presence of  
phthalocyanine and naphthalocyanine complexes of metals and ascorbic acid  
when simultaneously administered into a culture of cells

Inhibition of proliferation (%)			
	Human testicular carcinoma	Breast adenocarcinoma, MCF-7* line	Human lung carcinoma A-549**
10			
15	Co[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]	0	0
	Co[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]+AH <sub>2</sub>	52	83
20			
	Fe[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]	0	
	Fe[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]+AH <sub>2</sub>	12	
25			
	Fe[Pc(COONa) <sub>8</sub> ]	50	
	Fe[Pc(COONa) <sub>8</sub> ]+AH <sub>2</sub>	51	
30			
	Co[Pc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>6</sub> Cl <sup>⊖</sup> <sub>6</sub>	0	0
	Co[Pc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>6</sub> Cl <sup>⊖</sup> <sub>6</sub> +AH <sub>2</sub>	74	55
35			
	Co[Pc(SO <sub>3</sub> H) <sub>2</sub> ]	0	0
	Co[Pc(SO <sub>3</sub> H) <sub>2</sub> ]+AH <sub>2</sub>	76	30
40			
	Co[Pc(CH <sub>2</sub> (NH <sub>2</sub> ) <sub>2</sub> SCH <sub>2</sub> C <sup>18</sup> O <sub>8</sub> ]	0	
	Co[Pc(CH <sub>2</sub> (NH <sub>2</sub> ) <sub>2</sub> SCH <sub>2</sub> C <sup>18</sup> O <sub>8</sub> ]+AH <sub>2</sub>	64	
45			
	Co[Nc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>2</sub> ]Cl <sup>⊖</sup> <sub>2</sub>	0	
	Co[Nc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>2</sub> ]Cl <sup>⊖</sup> <sub>2</sub> +AH <sub>2</sub>	64	
50			
	Co[Pc(COONa) <sub>8</sub> ]	0	0
	Co[Pc(COONa) <sub>8</sub> ]+AH <sub>2</sub>	99.5	86

\* - method 1, [complex] = 5·10<sup>-5</sup>M, [AH<sub>2</sub>] = 1·10<sup>-4</sup>M.

\*\* - method 2, [complex] = 100 µg/ml, [AH<sub>2</sub>] = 227 µg/ml

55

Determination of antitumor activity of the drugs on mice with regrafted tumors (in vivo)

Tests were carried out on tumor strains: Ehrlich ascitic carcinoma (example 1), ascitic hepatoma 22 (examples 2,

3), solid breast adenocarcinoma Ca-755 (example 4).

The complexes are dissolved in a sterile physiological solution until a concentration of from 0.005 to 1% is obtained. Ascorbic acid is dissolved in sterile distilled water or an isotonic solution of sodium chloride to a concentration of from 0.011 to 2.2%. The complexes and ascorbic acid are administered intraperitoneally, intrapleurally, intravenously or into the tumor itself.

5 Example 1.

A tumor, an Ehrlich ascitic carcinoma, was grafted into mice intrapleurally. The tests were carried out in a manner 10 similar to that of Example 2.

Mice of the control group without treatment died on the 9th-15th day with development of tumorous pleurisy.

Mice, who had received treatment with a complex of  $\text{Co}[\text{Pc}(\text{COONa})_8]$  in a single dose of 75 mg/kg with subsequent administration of 165 mg/kg of ascorbic acid, lived for 18-40 days. Death from toxicity was not observed (Table 3).

15 Example 2.

A tumor, ascitic hepatoma 22, was grafted intraperitoneally, the grafting dose was  $10^6$  cells per mouse. Mice of both 20 sexes were used. The weight of each mouse was at least 18 g. Treatment was begun 48 hours after the tumor was grafted. Mice of the control group without treatment lived 19.3+1.7 days and died with expressed ascites. In the group of mice receiving treatment with a complex of  $\text{Co}[\text{Pc}(\text{COONa})_8]$  in a single dose of 100 mg/kg with subsequent administration of ascorbic acid (a course dose of 550 mg/kg), one mouse died on the 19th day with ascites, the remaining 8 of the 9 mice lived without symptoms of tumor for more than 70 days. Death from toxicity was not observed (Table 3).

Example 3.

25 Tests were carried out in a manner similar to that in example 1, but the tumor, ascitic hepatoma 22, was grafted to the mice intrapleurally.

Mice of the control group without treatment lived 5.7+1.6 days and died with exudation in the pleural cavity in a volume of about 2.0 ml.

30 In the group of mice who received treatment with a complex of  $\text{Co}[\text{Pc}(\text{COONa})_8]$  in a single dose of 75 mg/kg with subsequent administration of 165 mg/kg of ascorbic acid, the mice lived more than 70 days without symptoms of a tumor. Death from toxicity was not observed (Table 3).

35 Table 3

Effect of complex $\text{Co}[\text{Pc}(\text{COONa})_8]$ and ascorbic acid ( $\text{AH}_2$ ) on the life-span of mice with grafted tumors, as compared with the prototype				
Substance	Tumor strain			
	Ehrlich carcinoma		Hepatoma 22	
$\text{Co}[\text{Pc}(\text{COONa})_8]+\text{AH}_2$	296	0	370	70
$[\text{Cu}(\text{GGH})]\text{Cl}$ (prototype [5])	60	0		

Example 4.

50 Breast adenocarcinoma Ca-755 was grafted into the mice using 50 mg of tumorous tissue. Treatment was begun 48 hours or on the 9th day after the tumor was grafted. The complexes and ascorbic acid were administered in several ways: intravenously, intraperitoneally, intratumorously (Table 4).

55 The results obtained with mice having tumors were evaluated by means of generally accepted indexes of antitumor activity, with mice who were not given antitumor therapy being used for control.

Calculation of the increase of life-span was made using the equation:

$$ALS = \frac{L_{\text{test}} - L_{\text{control}}}{L_{\text{control}}} \times 100\%,$$

5 where L is the life-span in days.

Inhibition of tumor growth was calculated for solid tumors using the equation:

$$TGI = \frac{V_{\text{average control}} - V_{\text{average test}}}{V_{\text{average control}}} \times 100\%,$$

10

where  $V_{\text{average}}$  is the average volume of the tumor, calculated as the product of three measurements and expressed in cubic cm.

15 Regression of the tumor was determined for a developed solid adenocarcinoma Ca-755, the percentage of regression was calculated by the equation:

$$R = \frac{V_o - V_n}{V_o} \times 100\%,$$

20

where

R is the percentage of regression,

$V_o$  is the initial average volume of a tumor,

25  $V_n$  is the average volume of a tumor after treatment for "n" days.

30

Table 4

Inhibition of the growth of a solid breast adenocarcinoma Ca-755 after administration of phthalocyanine complexes of cobalt and ascorbic acid (AH <sub>2</sub> )		
Complex	Dose (mg/kg)	TGI*,%
Co[Pc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>6</sub> ]ClO <sub>6</sub>	25	58
AH <sub>2</sub>	27.5	38
Co[Pc(CH <sub>2</sub> C <sub>5</sub> H <sub>4</sub> N <sup>⊕</sup> ) <sub>6</sub> ]ClO <sub>6</sub> + AH <sub>2</sub>	25 + 27.5	91
Co[Pc(SO <sub>3</sub> Na) <sub>2</sub> ]	25	68
AH <sub>2</sub>	56.75	66
Co[Pc(SO <sub>3</sub> Na) <sub>2</sub> ] + AH <sub>2</sub>	25 + 56.75	88
Co[Pc(COONa) <sub>8</sub> ]	10	44
AH <sub>2</sub>	22	38
Co[Pc(COONa) <sub>8</sub> ] + AH <sub>2</sub>	10 + 22	61

\* - data in respect of Co complexes; Co[Pc(CH<sub>2</sub>C<sub>5</sub>H<sub>4</sub>N<sup>⊕</sup>)<sub>6</sub>]ClO<sub>6</sub> and Co[Pc(SO<sub>3</sub>Na)<sub>2</sub>] are presented for the 14th day, data in respect of the complex Co[Pc(COONa)<sub>8</sub>] are presented for the 16th day after transplantation of the tumors.

50

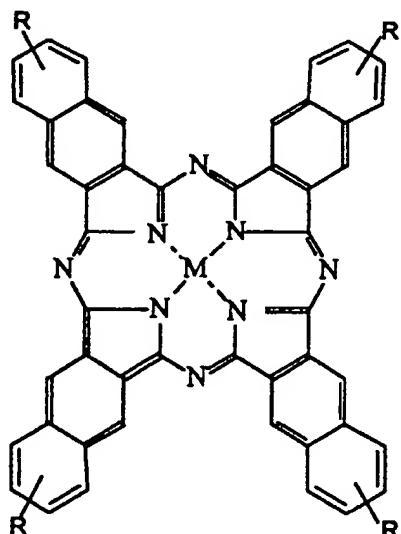
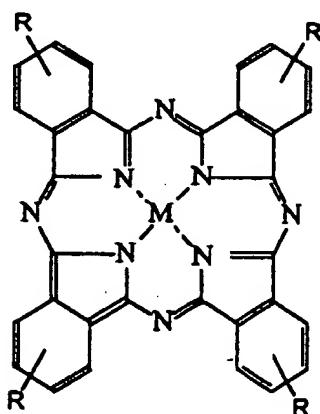
55 Thus, use of the proposed drug makes it possible to suppress effectively the growth of a wide range of malignant tumors, in particular to achieve the suppression of proliferation of cancer cells (in vitro) and inhibition of the growth of tumors in mice (in vivo) and substantially increase their life-span, including that obtained in comparison by use of the prototype.

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## Claims

1. Drug for tumor growth suppression, comprising a complex of a transition metal with a polydentate ligand and a  
 15 reductant, characterized in that it comprises a complex of cobalt or iron with substituted phthalocyanines or naph-  
 thalocyanines of the structural formula I or II:



I

II

45 where M = Co or Fe, R = COONa, SO<sub>3</sub>Na, CH<sub>2</sub>C<sub>5</sub>H<sub>4</sub>N<sup>⊕</sup>Cl<sup>⊖</sup>, CH<sub>2</sub>(NH<sub>2</sub>)<sub>2</sub>SCH<sub>2</sub>Cl and a biogenic reductant  
 with a ratio of the components from 1:5 to 1:50.

INTERNATIONAL SEARCH REPORT		International application No. PCT/RU 96/00060															
<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC <sup>6</sup> A61K 31/40 According to International Patent Classification (IPC) or to both national classification and IPC																	
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC <sup>6</sup> A61K 27/00, 31/40, C09B 47/04, C07D 487/22																	
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched																	
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)																	
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; padding: 2px;">Category*</th> <th style="text-align: left; padding: 2px;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="text-align: left; padding: 2px;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">WO, A, 95/05818 (THE SECRETARY OF STATE FOR DEFENCE), 02 March 1995 (02.03.95), the abstract</td> <td style="padding: 2px; text-align: center;">1</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">US, A, 5358940 (CIBA-GEIGY CORPORATION), 25 October 1994 (25.10.94), the abstract</td> <td style="padding: 2px; text-align: center;">1</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">US, A, 4393071 (NAOHARU FUJII), 12 July 1983 (12.07.83)</td> <td style="padding: 2px; text-align: center;">1</td> </tr> <tr> <td style="padding: 2px;">A</td> <td style="padding: 2px;">EP, A1, 0484027 (IMPERIAL CHEMICAL INDUSTRIES PLC), 06 May 1992 (06.05.92), the description, page 8, claims nos. 12-13</td> <td style="padding: 2px; text-align: center;"></td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	WO, A, 95/05818 (THE SECRETARY OF STATE FOR DEFENCE), 02 March 1995 (02.03.95), the abstract	1	A	US, A, 5358940 (CIBA-GEIGY CORPORATION), 25 October 1994 (25.10.94), the abstract	1	A	US, A, 4393071 (NAOHARU FUJII), 12 July 1983 (12.07.83)	1	A	EP, A1, 0484027 (IMPERIAL CHEMICAL INDUSTRIES PLC), 06 May 1992 (06.05.92), the description, page 8, claims nos. 12-13	
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<input type="checkbox"/> Further documents are listed in the continuation of Box C.		<input type="checkbox"/> See patent family annex.															
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Date of the actual completion of the international search		Date of mailing of the international search report															
06 June 1996 (06.06.96)		11 June 1996 (11.06.96)															
Name and mailing address of the ISA/ RU Facsimile No.		Authorized officer  Telephone No.															

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